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Smoking Status and Long-Term Survival After First Acute Myocardial Infarction

A Population-Based Cohort Study

Yariv Gerber, PHD,* Laura J. Rosen, PHD,† Uri Goldbourt, PHD,* Yael Benyamini, PHD,§ Yaacov Drory, MD,‡ for the Israel Study Group on First Acute Myocardial Infarction

Tel Aviv, Israel

Objectives We compared long-term survival after acute myocardial infarction (AMI) of never-smokers, pre-AMI quitters, post-AMI quitters, and persistent smokers and assessed whether cigarette reduction among persistent smokers is associated with lower mortality.

Background Quitting smoking has been shown to improve outcome after AMI. However, longitudinal cohort data with repeated assessments of smoking and information on multiple confounders are lacking. Moreover, little is known about the importance, if any, of reductions in the amount smoked.

Methods Consecutive patients ≤65 years of age, discharged from 8 hospitals in central Israel after first AMI in 1992 to 1993, were followed through 2005. Extensive data, including self-reported smoking habits, were obtained at baseline and 4 times during follow-up. Cox proportional hazards regressions were used to assess the hazard ratios (HRs) for death associated with smoking categories modeled as time-dependent variables.

Results At baseline, smokers were younger, more likely to be male, and had a lower prevalence of hypertension and diabetes than nonsmokers. Over a median follow-up of 13.2 years, 427 deaths occurred in 1,521 patients. The multivariable-adjusted HRs for mortality were 0.57 (95% confidence interval [CI]: 0.43 to 0.76) for never-smokers, 0.50 (95% CI: 0.36 to 0.68) for pre-AMI quitters, and 0.63 (95% CI: 0.48 to 0.82) for post-AMI quitters, compared with persistent smokers. Among persistent smokers, upon multivariable adjustment including pre-AMI intensity, each reduction of 5 cigarettes smoked daily after AMI was associated with an 18% decline in mortality risk ($p < 0.001$).

Conclusions Smoking cessation either before or after AMI is associated with improved survival. Among persistent smokers, reducing intensity after AMI appears to be beneficial. (J Am Coll Cardiol 2009;54:2382–7) © 2009 by the American College of Cardiology Foundation

Smoking is a well-established risk factor for cardiovascular disease (CVD) development (1,2) and is included in the Framingham prediction score (3). Paradoxically, a lower case-fatality rate associated with smoking shortly after acute myocardial infarction (AMI) has been commonly reported (4–6). However, this "smoker's paradox" is largely attributable to the younger age and better CVD profile of AMI smokers compared with nonsmokers. Longer-term prospective investigations have clearly demonstrated considerable mortality risk reduction associated with smoking cessation after AMI (7,8). However, methodological limitations inherent in the current published data leave uncertainties about key issues. Indeed, previous studies were mostly small in size and limited in follow-up period (up to 10 years), were often unable to ascertain whether former smokers quit before or after the AMI, and have not adequately controlled for essential confounding factors (reviewed in [7–9]). In addition, there is an ongoing debate whether smoking reduction improves outcome in the general population, and conflicting results have been reported (10–12). Moreover, to this end, no data are available on smoking reduction and outcome after AMI. Lastly, a few studies have incorporated regular assessment of smoking status during follow-up. This is critical, given earlier reports of long-term repeated cycles of smoking abstinence and relapse after AMI (13), which might result in substantial misclassification.

With data from a prospective population-based cohort study of incident AMI patients with repeated assessments of smoking, our goals were: 1) to evaluate long-term survival of

From the Departments of *Epidemiology and Preventive Medicine, †Health Promotion, School of Public Health, and ‡Rehabilitation, Sackler Medical School, and the §Bob Shapell School of Social Work, Tel Aviv University, Tel Aviv, Israel. This work was supported in part by the Israel National Institute for Health Policy and Health Services Research.

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never-smokers, pre-AMI quitters, post-AMI quitters, and persistent smokers; and 2) to examine whether cigarette reduction is associated with lower mortality risk.

Methods

Study design and setting. The Israel Study of First Acute Myocardial Infarction is a longitudinal, prospective investigation of the role of sociodemographic, medical, and psychosocial variables measured in patients hospitalized with incident (i.e., first-ever) AMI in long-term clinical outcomes, psychosocial adjustment, and quality of life (14–16). Between February 15, 1992, and February 15, 1993, a total of 1,626 consecutive AMI patients 65 years of age or less were admitted to 8 Israeli medical centers. These hospitals provide care to the entire population of central Israel. Of these patients, 81 (5%) died during hospital stay, leaving 1,545 eligible candidates for the study, among whom 1,521 (98%) consented to participate and completed the follow-up.

The diagnosis of AMI was established by the presence of at least 2 of the following criteria: 1) characteristic chest pain lasting at least 20 min; 2) creatine kinase elevation ≥1.5 times the upper limit of normal or creatine kinase myocardial band fraction >5% when simultaneous reference creatine kinase levels exceeded the upper limit of normal; and 3) electrocardiographic changes compatible with Q-wave or non–Q-wave AMI. All diagnoses were verified by an experienced cardiologist (Dr. Drory). Subjects with prior infarction were excluded.

Data at study entry and during follow-up were obtained through structured interviews, psychosocial questionnaires, and review of the entire medical record. A comprehensive clinical follow-up was performed through December 31, 2005. Participants were interviewed 5 times: before discharge (T1) and at 3 to 6 months (T2), 1 to 2 years (T3), 5 years (T4), and 10 to 13 years (T5) after AMI. All aspects of the study were approved by the appropriate institutional review boards.

Smoking status assessment. Data on smoking were obtained with structured interviews. Smoking habits including intensity (number of cigarettes smoked/day), duration (years of smoking), and time since cessation (if applicable) were reported at T1, with the former reassessed at all follow-up interviews (T2 to T5). In the initial interview (approximately 1 week after the index AMI), patients were asked about their smoking habits before the event. In the following interviews, the questions referred to both present smoking behavior and smoking habits since last interview. Patients were categorized into never-smokers, pre-AMI quitters, post-AMI quitters, and persistent smokers. Pre-AMI quitting was defined as abstinence for more than 6 months before the index AMI (17). Intermittent smoking between interviews was classified as smoking (18).

Sociodemographic variables. Demographic and socioeconomic status (SES) measures were self-reported and included the following variables: origin (classified as Mid-Eastern vs. North American/Israeli), family income relative to the national average (categorized as below average, average, and above average), education (years of schooling), and employment before the index AMI (dichotomized as part- or full-time employment vs. none).

Abbreviations and Acronyms

AMI = acute myocardial infarction
CABG = coronary artery bypass surgery
CI = confidence interval
CVD = cardiovascular disease
HR = hazard ratio
IQR = interquartile range
PTCA = percutaneous transluminal coronary angioplasty
RR = relative risk
SES = socioeconomic status

Clinical variables. Clinical data were reviewed and verified by a senior cardiologist. The entire inpatient and outpatient medical records and data obtained through structured detailed interviews were used to ascertain CVD risk factors, AMI characteristics and severity indexes, and co-interventions. Measurements recorded at the index hospital stay or at the closest time before or after the index date were considered. Obesity was defined as body mass index ≥30 kg/m^2. Diabetes, hypertension, and dyslipidemia were defined clinically. Leisure time physical activity was self-reported and dichotomized into active versus nonactive in the year before the index AMI. Comorbidity was assessed by the Charlson index (19) and analyzed categorically (no comorbidity for 0 points, moderate comorbidity for 1 to 2 points, and severe comorbidity for 3 points or more). The AMI characteristics and severity indexes included infarct type and location, and Killip class. Reperfusion therapy and revascularization included thrombolysis, percutaneous transluminal coronary angioplasty (PTCA), and coronary artery bypass grafting (CABG). Early revascularization referred to procedures performed within 45 days of the index date. Cardiovascular events occurring during follow-up (recurrent AMI, unstable angina pectoris, heart failure, PTCA, and CABG) were also considered.

Mortality assessment. Mortality follow-up began at the date of the index hospital stay and lasted through December 31, 2005 (median 13.2 years; interquartile range [IQR] 12.0 to 13.5 years). Death was ascertained through various sources, including data from the Israeli Population Registry, death certificates, hospital charts, family physicians, and family members.

Statistical analyses. Data are presented as percentage, mean ± SD, or median (IQR). Baseline characteristics across smoking categories were compared by the chi-square test for categorical variables and analysis of variance for continuous variables.

Cox proportional hazards models (20) were constructed to evaluate the hazard ratios (HRs) and 95% confidence intervals (CIs) for death associated with smoking categories handled as time-dependent covariates. These regressions model the effects of subjects transferring from one exposure group to another. Initial adjustment was made for age and

sex. A subsequent model additionally adjusted for SES measures (origin, education, income, and employment status), traditional risk factors (hypertension, dyslipidemia, diabetes, obesity, and physical inactivity), AMI characteristics and severity indexes (Q-wave AMI, anterior AMI, Killip class, and comorbidity score), and co-interventions (thrombolysis and early revascularization procedures). Lastly, a fully adjusted model further controlled for CVD events occurring during follow-up (recurrent AMI, CABG, PTCA, unstable angina pectoris, and heart failure) modeled as time-dependent covariates. In a complementary analysis, random-effects Cox models were examined (21), accounting for potential intra-hospital correlation. This analysis yielded virtually identical results as the fixed-effects models, suggesting negligible random medical center effects in these data. The proportional hazards assumption was tested with the Schoenfeld residuals, with no violations detected. There were no missing values in the covariates used in the regression analyses, except for family income (17%) and pre-AMI physical activity (8%), for which indicator variables representing unknown values were included when appropriate. All p values were 2-tailed.

Results

The analysis was based on 1,521 first AMI patients, with a mean age of 54 ± 8 years at the index date and 19% women. One-half of the participants (50%) had <12 years of education, 47% rated their family income as below average, and 76% were employed before the index AMI. Baseline smoking categories included never-smokers (n = 418, 27.5%), former smokers (n = 305, 20.0%), and smokers (n = 798, 52.5%; men, 56.4%, women, 35.6%). For former smokers, the median abstinence duration at the index AMI was 10 (IQR 5 to 18) years. Among smokers at AMI, the average number of cigarettes smoked/day was 31 ± 16—32 ± 17 men versus 26 ± 13 for women. The baseline characteristics across smoking categories are presented in Table 1. On average, smokers were younger, more likely to be male, had lower prevalence of hypertension and diabetes, and were less frequently engaged in leisure-time physical activity than nonsmokers. Former smokers were characterized by a more favorable SES profile compared with other categories.

Among smokers at the index date, the point abstinence rates among survivors were 70% at T2, 62% at T3, 55% at T4, and 59% at T5. The respective continuous abstinence rates were 59% at T3, 44% at T4, and 35% at T5.

Long-term survival by smoking category. Over a total of 17,453 person-years of follow-up, 427 patients died (n = 123 never-smokers, n = 70 former smokers, and n = 234 current smokers according to baseline classification), of which 302 (71%) were cardiac deaths. Overall survival differed substantially among the smoking categories (Table 2). In a Cox

Table 1 Baseline Characteristics by Smoking Category

Characteristics	Overall	Never-Smokers	Former Smokers	Current Smokers	p Value
n	1,521	418	305	798	
Age, yrs	54 ± 8	56 ± 7	56 ± 7	52 ± 8	<0.001
Male	81	62	91	87	<0.001
Mid-Eastern origin	32	31	27	35	0.03
Education, yrs	11.0 ± 4.3	10.8 ± 4.7	12.0 ± 4.2	10.7 ± 4.0	<0.001
Family income					<0.001
Above average	25	24	34	27	
Average	28	23	29	35	
Below average	47	53	37	38	
Pre-AMI employment	76	65	82	79	<0.001
Anterior AMI	42	46	37	43	0.09
Q-wave AMI	75	69	73	78	0.002
Killip class >1	21	24	20	20	0.13
Comorbidity index, points					0.54
0	61	60	62	62	
1–2	35	35	33	35	
≥3	4	6	5	4	
Hypertension	38	50	44	29	<0.001
Diabetes	25	30	30	20	0.001
Dyslipidemia	37	40	38	34	0.14
Obesity	19	22	17	18	0.12
Pre-AMI physical activity	26	28	33	22	0.001
Thrombolysis	41	35	39	45	0.004
CABG within 45 days	6	7	9	5	0.02
PTCA within 45 days	17	17	21	16	0.24

Values are mean ± SD or % unless otherwise indicated.
AMI = acute myocardial infarction; CABG = coronary artery bypass surgery; PTCA = percutaneous transluminal coronary angioplasty.

Table 2 Long-Term Mortality Risk After First AMI Associated With Smoking Categories Modeled as Time-Varying Covariates

Smoking Categories	Hazard Ratio (95% CI) for Death			
	Unadjusted	Age- and Sex-Adjusted	Multivariable-Adjusted*	Multivariable-Adjusted†
Never-smokers	0.78 (0.61–1.00)	0.54 (0.42–0.71)	0.57 (0.43–0.75)	0.57 (0.43–0.76)
Pre-AMI quitters	0.57 (0.43–0.77)	0.43 (0.32–0.57)	0.52 (0.37–0.71)	0.50 (0.36–0.68)
Post-AMI quitters	0.60 (0.46–0.78)	0.55 (0.42–0.72)	0.60 (0.45–0.79)	0.63 (0.48–0.82)
Persistent smokers	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)

*Adjusted for age, sex, origin (Mid-Eastern vs. North American/Israeli), education (years of schooling), income (below average, average, and above average), pre-AMI employment, hypertension, dyslipidemia, diabetes, obesity, physical activity, Q-wave AMI, anterior AMI, Killip class (1 vs. ≥2), comorbidity (none, moderate, and severe), thrombolysis, CABG, and PTCA. †Further adjusted for recurrent AMI, CABG, PTCA, unstable angina pectoris, and heart failure occurring during follow-up (modeled as time-varying covariates).

CI = confidence interval; other abbreviations as in Table 1.

regression with smoking categories modeled as time-varying covariates—after adjustment for SES measures, traditional risk factors, AMI characteristics and severity indexes, and cointerventions—the HRs for death were 0.57 (95% CI: 0.43 to 0.75) for lifelong nonsmoking, 0.52 (95% CI: 0.37 to 0.71) for pre-AMI quitting, and 0.60 (95% CI: 0.45 to 0.79) for post-AMI quitting, compared with persistent smoking (all $p < 0.001$). Further adjustment for CVD events occurring during follow-up yielded respective HRs of 0.57 (95% CI: 0.43 to 0.76), 0.50 (95% CI: 0.36 to 0.68), and 0.63 (95% CI: 0.48 to 0.82) (Fig. 1). In pairwise comparisons, no significant differences were detected among never-smokers, pre-AMI quitters, and post-AMI quitters (all p values > 0.20).

Comparably, the estimated effect sizes for being normotensive (HR: 0.74, 95% CI: 0.60 to 0.91) or nondiabetic (HR: 0.67, 95% CI: 0.53 to 0.83) and for undergoing PTCA (HR: 0.58, 95% CI: 0.44 to 0.76) were similar or smaller than that of quitting smoking.

Smoking reduction and long-term survival. Among persistent smokers (n = 381; 115 deaths), after multivariable adjustment for baseline characteristics (including SES measures, traditional risk factors, AMI characteristics and severity indexes, and co-interventions) and pre-AMI intensity, each reduction of 5 cigarettes smoked/day after the AMI (i.e., average consumption during T2 to T4) was associated with an 11% decline (95% CI: 3% to 19%, $p = 0.01$) in mortality risk. Further adjustment for CVD events occurring during follow-up yielded an estimated decline of 18% (95% CI: 9% to 25%, $p < 0.001$).

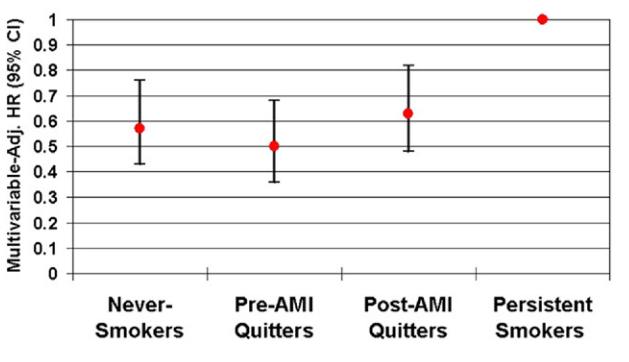

Figure 1 Multivariable-Adjusted HRs (95% CIs) of Death for Smoking Categories

Adjusted association between smoking categories modeled as time-varying covariates and long-term mortality after acute myocardial infarction (AMI) (see final model for the variables controlled for in Table 2). CI = confidence interval; HR = hazard ratio.

Discussion

The primary finding of this study is that lifetime nonsmoking and quitting before or after initial AMI confer survival benefits on post-MI patients. Among survivors of initial AMI, never-smokers had roughly one-half the risk of dying than those who continued to smoke after AMI. Those smokers who quit before AMI and those who quit after AMI significantly decreased their risk of dying, as compared with persistent smokers (pre-AMI quitters: HR: 0.50; 95% CI: 0.36 to 0.68; post-AMI quitters: HR: 0.63; 95% CI: 0.48 to 0.82). Furthermore, reduction of daily cigarettes among those who continued to smoke was associated with higher survival (each reduction of 5 cigarettes smoked/day after AMI was associated with an 18% [95% CI: 9% to 25%] decline in mortality risk).

At the time of enrollment in 1992 to 1993, 53% of patients were current smokers (men, 56%; women, 36%), 20% were former smokers, and 27% were never-smokers. Thus, smoking prevalence in this population was considerably higher than the prevalence of smoking in the Israeli population (1992 data: Jewish men, 41%; Jewish women, 29%) (22) and suggests that smokers are overrepresented among AMI victims.

Of those smokers who underwent AMI, the point abstinence rates throughout the follow-up were 50% to 70%. Furthermore, more than one-third (35%) were continuously abstinent for at least 10 years. These numbers are consistent with previous reports that 28% to 74% of smokers quit after AMI (23,24). Our numbers on successful cessation after AMI suggest a relatively low recidivism rate, which produces an unusually high long-term success rate for quitting smoking. By comparison, according to current U.S. documents (25), approximately 44% of smokers attempt to quit annually, but only 4% to 7% succeed.

Benefit of quitting: compare strength of association with that of other studies. The benefits of quitting smoking among individuals in the general population and among patients with coronary heart disease are well documented. Although the exact toxic components of cigarette smoke and the potential mechanisms leading to cardiovascular dysfunction remain to be determined, clinical and experimental studies indicate that smoking promotes lipid oxidation, inflammation, and thrombosis, with oxidative stress playing a pivotal mechanistic role (26). The landmark study of British physicians by Doll et al. (2) showed that quitting throughout life conferred survival advantages. Those smokers who quit early had larger gains in life expectancy. Those who quit by age 30 years avoided most of the added risk, cessation at age 50 years halved the additional hazard, and even quitting at age 60 years conferred significant survival advantage. Notably, a lower age-standardized mortality rate was demonstrated in that study in former versus current smokers for all principal CVD categories (i.e., ischemic heart disease, cerebrovascular disease, and other vascular disease). In a systematic review, Critchley and Capewell (8) found that cardiac patients who quit smoking reduced their risks by 36% (relative risk [RR]: 0.64, 95% CI: 0.58 to 0.71), with reductions ranging from 7% to 66% (on the basis of crude RRs). Wilhelmsen (22) found that reductions in mortality caused by stopping smoking among patients with coronary disease varied from 38% to 70%. Wilson et al. (7) reviewed the published data for the effect of cessation on mortality after infarction and found that the RR reductions in mortality ranged from 15% to 61%, with a combined RR estimate of 0.54 (95% CI: 0.46 to 0.62). Thus, our figures of reduced mortality risk of 50% for those who quit pre-AMI and 37% reduction in mortality risk for those who quit after AMI are consistent with figures found in shorter-term investigations.

Does reduction help? Although there has been extensive research performed on the benefits of quitting, study of the benefits accrued from reduction of smoking has received somewhat less attention. Previous findings showing a monotonic dose–response relationship between number of cigarettes smoked and mortality (27) suggest that reduction in the number of cigarettes might lead to reduced risk of mortality. However, in the few published studies of smoking reduction and mortality (10,12), the hypothesized positive effect of reduction on mortality has not been borne out. No differences in all-cause mortality between reducers and sustained heavy smokers were observed in large prospective cohort studies conducted in Copenhagen (10) and Norway (12). The results of both of these studies conflict with our data.

There are several possible explanations for differences in the results. First, the study populations were different. The Norwegian (Tverdal) study was based on a population cohort that excluded individuals with previous AMI. The Copenhagen (Godtfredsen) study was based on 3 population cohorts and not restricted to post-AMI patients. Therefore, 1 possible explanation for the differences in findings is that the benefits of reduction for post-AMI individuals do not exist in the general, healthier population. A second difference concerns definition of reducers: in both the Tverdal and Godtfredsen studies, "reducers" were defined as individuals who had reduced smoking by at least 50%. Our study, by contrast, used reported numbers of cigarettes smoked at each time point. If a dose–response relationship exists between amount of reduction and mortality, our study had greater power to detect an effect than the 2 previous studies. A third explanation for the differences in the results is that smoking reduction in the general population might be associated with poor health status, with true gains in life expectancy due to reduction masked by the higher risk profile of reducers. Because our study participants were all post-AMI, the underlying risk profile of reducers and non-reducers might have been more similar than the comparative profiles of reducers and non-reducers in the general population, thus allowing a less-biased comparison.

Methodological considerations. The present study shares the methodological challenges of other similar research and overcomes some although not all of the challenges. Like other studies on this topic, ours was observational in nature. Thus, any observed associations could be attributable to other, unmeasured variables such as concomitant changes in other health-related behaviors (e.g., adoption of better eating habits) or unequal distribution of co-interventions among the smoking categories. Such confounding would be less likely to occur in a randomized trial; however, such a trial would be unethical, because it would require assigning some individuals to persistent smoking.

The study results are applicable to community patients ages 65 years or less who underwent incident AMI—thereby highly generalizable. Nevertheless, because patients who died during the index hospital stay were excluded, some survivor bias might exist. The follow-up period of 13 years was long compared with follow-up periods in other studies: the Wilson meta-analysis found a range of 2 to 10 years of follow-up, mostly <6 years (7).

An important advantage that this study has over other studies is that smoking status was ascertained repeatedly over time. Most of the studies (7,8) assess smoking at only 1 time point, and many of the authors note the consequent problem of misclassification of smoking status due to recidivism. The 5 repeated time points over a period of more than 1 decade might provide a more accurate picture of true smoking habits in this study than would be possible from evaluation at a single point. Furthermore, inclusion of smoking status as well as other important confounders as time-dependent covariates in the regression models ensures appropriate analysis of these key variables. Thus, the methodology used in this paper might overcome some although not all of the problems of recidivism and misclassification faced by other authors.

Most previous studies were unable to differentiate between pre- and post-AMI quitters (8). Our methodology allowed us to differentiate between these groups and so isolate the benefit of quitting after AMI. Thus, we provide

empirical evidence in support of cessation interventions at this important juncture.

An additional limitation of this study is that, like most similar studies, it relied on self-report of smoking status. In a recent meta-analysis of cohort studies (7), only 1 of 12 studies used biochemical validation of smoking status. That review noted that self-report of smoking status among post-AMI patients might be misrepresented by as many as 26% of the patients. Such misclassification might bias the results in an unknown direction.

The present study suggests that quitting smoking before AMI is associated with reduced mortality risk of 50%, whereas quitting after AMI is associated with reduced mortality risk of 37%, compared with persistent smoking. As noted previously (8), these reductions seem at least as great as other secondary preventive therapies, such as lowering cholesterol levels (a 29% reduction) (28), aspirin (15%) (29), and beta-blockers (23%) (30). Furthermore, the survival benefit associated with smoking cessation seen in this study was similar to that of undergoing PTCA and greater than those of being normotensive or nondiabetic.

Conclusions

Continuing to smoke after an AMI reduces life expectancy. Smokers who have had a heart attack should be provided with appropriate interventions to help them quit.

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Reprint requests and correspondence: Dr. Yariv Gerber, Department of Epidemiology and Preventive Medicine, School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Tel Aviv 69978, Israel. E-mail: yarivg@post.tau.ac.il.

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Key Words: cigarette reduction ■ cohort studies ■ epidemiology ■ myocardial infarction ■ secondary prevention ■ smoking ■ survival.